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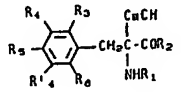
(54) α-Acetylenic Amino Acids

(57) Pharmaceutically useful compounds have the formula



wherein R_1 is hydrogen, (C_{1-4}alkyl) carbonyl, (C_{1-4}alkoxy) carbonyl or CO-CHNH$_2$-R_{27} wherein R_{27} is hydrogen, alkyl of 1 to 4 carbon atoms, benzyl or *p*-hydroxybenzyl; R is hydroxy, alkoxy of 1 to 8 carbon atoms, -NR_7R_8 wherein R_7 and R_8 are the same or different and are each hydrogen or C_{1-4} alkyl, or NH-CHR_9-COOH wherein R_9 is hydrogen, alkyl of 1 to 4 carbon atoms, benzyl or *p*-hydroxybenzyl; and R_2, R_3, R_4, R_5 and R_6 are certain combinations of hydrogen, methyl, ethyl, *tert*-butyl, chlorine, fluorine and OR_{10} wherein R_{10} is hydrogen, alkyl of 1 to 8 carbon atoms, (C_{1-6}alkyl) carbonyl, benzoyl or phenyl (C_{1-6}alkyl) carbonyl or R_3 and R_4 together are methylene dioxy.

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SPECIFICATION

α-Acetylenic amino acids

This invention relates to novel pharmaceutically useful α-acetylenic amino acid derivatives which are inhibitors of aromatic amino acid decarboxylase.

BACKGROUND OF INVENTION

The amino acids tryptophan, 5-hydroxy- tryptophan, 3,4-dihydroxy- phenylalanine (DOPA), tyrosine and phenylalanine are metabolically converted to tryptamine, 5-hydroxy- tryptamine, 3,4-dihydroxy-phenethylamine or dopamine, tyramine and phenethylamine respectively by an aromatic amino acid decarboxylase. It is believed that the aromatic amino acid decarboxylase enzyme is non-specific, particularly, insofar as peripheral catalysis is concerned. Evidence does exist, however, to indicate that in the brain specific decarboxylation enzymes exist for each of DOPA and 5-hydroxy- tryptophan.

The above-enumerated aromatic amines are known to be involved in various pathophysiological processes. For example, it has been found that tryptamine, the decarboxylation production of tryptophan is enzymatically methylated to monomethyl- tryptamine which in turn is methylated enzymatically to dimethyl-tryptamine (DMT) in human red blood cells, plasma and platelets. The methylating enzyme is present in many mammalian species and has been shown to be produced in brain tissues of several species including man. DMT which has strong hallucinogenic or psychomimetic properties may play a role in the etiology of schizophrenia and other psychotic disorders. Hence any agent which would block formation of DMT may be useful as an antipsychotic agent. Blocking the decarboxylation of tryptophan results in decreased levels of tryptamine, removing the substrate for DMT formation. Hence an inhibitor of aromatic amino acid decarboxylase which would block conversion of tryptophan to tryptamine may be useful as an antipsychotic agent.

Both 5-hydroxy- tryptamine (5-HT), the decarboxylation product of 5-hydroxy- tryptophane, and 3,4-dihydroxy- phenethyl- amine (dopamine) the decarboxylation product of DOPA are involved in peripheral and central physiological processes, and agents which are effective in the control of levels of these amines have resulted in useful pharmacological agents. It has been shown that central or brain levels of 5-HT and norepinephrine, which is formed metabolically by hydroxylation of dopamine, are higher in patients with manic disorders than in individuals without such disorders. It has also been shown that agents which decrease central levels of monoamines, for example, 5-HT and particularly norepinephrine have antimanic properties which given to human subjects, whereas drugs that increase monoamine levels could precipitate mania in susceptible individuals. Hence, agents which block formation of 5-HT and dopamine, such as, for example, by inhibiting the aromatic amino acid decarboxylase enzyme which converts 5-hydroxy- tryptophan and DOPA to 5-HT and dopamine respectively may be useful as antipsychotic agents or major tranquilizers in treating manic disorders.

It has also been shown that agents useful in inhibiting the decarboxylation of DOPA to dopamine are useful in the treatment of Parkinsonism when administered concurrently with exogenous DOPA or L-DOPA. It is believed that Parkinsonism is due, at least in part, to decreased central levels of dopamine since exogenous administration of DOPA or L-DOPA is known to be an effective means of treating Parkinsonism. However, since exogenously administered DOPA is readily converted enzymatically to dopamine peripherally it is necessary to administer large amounts in order to have increased absorption centrally. DOPA readily penetrates the blood-brain barrier whereas dopamine does not. Administration of DOPA or L-DOPA in conjunction with a peripherally active inhibitor of the enzyme which converts DOPA to dopamine reduces the amount of L-DOPA that must be administered in order to have adequate circulating levels for central absorption. Other advantages are also realized by administration of an aromatic amino acid decarboxylase inhibitor along with L-DOPA. By preventing formation of dopamine peripherally, side effects attributed to dopamine such as, cardiac arrhythmia, nausea and vomiting may be avoided.

Studies indicate that levels of 5-hydroxy- tryptamine (5-HT) are lower in patients with depressive syndromes than in individuals without such syndromes. Also, administration of exogenous L-5-hydroxy- tryptophan (L-5-HTP) is effective in treating certain depressed patients. However, as with DOPA, since L-5-HTP is readily metabolized peripherally to 5-HT it is necessary to administer large amounts of L-5-HTP in order to achieve increased central levels of the amino acid. It has been shown that by administering an inhibitor of the aromatic amino acid decarboxylase enzyme that catalyzes the formation of 5-HT from 5-HTP peripherally the amount of exogenous 5-HTP required to give increased central levels is markedly reduced. In other words inhibitors of aromatic amino acid decarboxylase when used in conjunction with exogenous 5-HTP have been shown to be useful in treating depression.

Agents which block peripheral conversion of 5-HTP to 5-HT may be useful in treating other conditions which respond to increased central levels of 5-HTP as a result of exogenous administration of 5-HTP. I has been shown that exogenous L-5-HTP is useful in treating action myoclonus. Also, studies reveal that administration of exogenous 5-HTP is useful in treating insomnia. Hence concurrent administration of 5-HTP and an aromatic amino acid decarboxylase inhibitor may be beneficial in treating these conditions.

Blocking peripheral formation of 5-hydroxy- tryptamine may result in other beneficial effects since it is known that 5-HT is involved, for example, in the etiology of rheumatoid arthritis and the carcinoid syndrome by increasing collagen levels. Also, it is reported that 5-HT is the primary autocoid responsible for anaphylactoid reactions in human subjects as well as bronchoconstriction in asthmatic human subjects, and agents

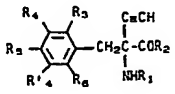
which antagonize or inhibit formation of 5-HT are useful in treating these conditions. 5-HT is known to cause platelet aggregation and has been implicated as a causal factor in the post-gastrectomy dumping syndrome and migraine headache. Methylsergide, a 5-hydroxy- tryptamine antagonist, has proven effective in treating post-gastrectomy dumping syndrome.

It has been suggested that phenethylamine, the decarboxylation product of phenylalanine, as an endogenous compound contributes to schizophrenic symptoms and triggers migraine headaches. Also, it has been suggested that endogenous tyramine, the decarboxylation product of tyrosine, contributes to seizure disorders.

Hence, it is readily evident that agents which are useful in regulating the levels of aromatic amino acids and amines find use in many pharmacological situations. The compounds of the present invention are inhibitors of the aromatic amino acid decarboxylase which converts tryptophan, 5-hydroxy- tryptophan, 3,4-dihydroxy- phenylal- anine, tyrosine and phenylalanine to the respective amines and hence provide useful pharmacologic agents.

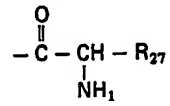
SUMMARY OF INVENTION

The compounds of the present invention are represented by the following general Formula:

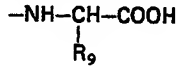


Formula I

In the above general Formula I R_1 is selected from hydrogen, alkylcarbonyl wherein the alkyl moiety has from 1 to 4 carbon atoms and is straight or branched, alkoxycarbonyl wherein the alkoxy moiety has from 1 to 4 carbon atoms and is straight or branched and



wherein R_{27} is selected from hydrogen, a straight or branched lower alkyl group of from 1 to 4 carbon atoms, benzyl and *p*-hydroxybenzyl; R_2 is selected from hydroxy, a straight or branched alkoxy group of from 1 to 8 carbon atoms, $-NR_7R_8$ wherein each of R_7 and R_8 is hydrogen or a straight or branched alkyl group of from 1 to 4 carbon atoms, and



wherein R_9 is hydrogen, a straight or branched lower alkyl group of from 1 to 4 carbon atoms, benzyl and *p*-hydroxybenzyl; each of R_3, R_4, R_5, R'_4 and R_6 has the meaning defined in the following Table 1 wherein R_{10} is hydrogen, a straight or branched alkyl group of from 1 to 8 carbon atoms, alkylcarbonyl wherein the alkyl moiety is straight or branched and has from 1 to 6 carbon atoms, benzoyl or phenylalkylene- carbonyl wherein the alkylene moiety is straight or branched and has from 1 to 6 carbon atoms:

TABLE I

R_3	R_4	R_5	R'_4	R_6
H	$-O-CH_2-O-$		H	H
H	H	H	H	H
H	H	OR_{10}	H	H
H	OR_{10}	H	H	H
H	OR_{10}	OR_{10}	H	H
OR_{10}	H	Cl	H	H
H	OR_{10}	Cl	H	H
Cl	OR_{10}	H	H	H
Cl	OR_{10}	Cl	H	H
Cl, F	H	OR_{10}	H	H
Cl	H	H	H	CH_3
Cl	H	Cl	H	CH_3
H	H	Cl, F	H	CH_3
OR_{10}	H	CH_3	H	CH_3
Cl	H	CH_3	H	CH_3
H	H	OR_{10}	H	CH_3
H	H	OR_{10}	H	C_2H_5
OR_{10}	H	C_2H_5	H	C_2H_5
H	OR_{10}	H	OR_{10}	H
H	OR_{10}	OR_{10}	OR_{10}	H
H	H	OCH_3	OH	H
H	H	OH	OCH_3	H
OR_{10}	OR_{10}	H	H	H
OR_{10}	H	H	H	H
H	H	Cl	H	C_2H_5
H	H	Cl	H	tert-C_4H_9
H	H	OR_{10}	H	tert-C_4H_9

Pharmaceutically acceptable salts and individual optical isomers of the compounds of general Formula I are also included within the scope of this invention.

The compounds of general Formula I are useful pharmacological agents in that said compounds are inhibitors of aromatic amino acid decarboxylase and useful as intermediates in the preparation of useful pharmacological agents.

DETAILED DESCRIPTION OF INVENTION

In the above general Formula I the term alkylcarbonyl is taken to mean the group alkyl–$\overset{O}{\overset{\|}{C}}$– wherein the alkyl moiety has from 1 to 6 carbon atoms and is a straight chain or branched chain.

The term benzoyl as used in general Formula I means the group

The term phenylalkylene- carbonyl as used in general Formula I is taken to mean the group

wherein the alkylene moiety has from 1 to 6 carbon atoms and is a straight chain or a branched chain, illustratively, methylene, ethylene, isopropylene and butylene.

Illustrative examples of straight or branched alkoxy groups having from 1 to 8 carbon atoms as used herein are methoxy, ethoxy, isopropoxy, *n*-butoxy, *tert*-butoxy, *n*-pentyloxy, *tert*-pentoxy, *n*-hexyloxy and *n*-octyloxy.

Illustrative examples of straight or branched alkyl groups having from 1 to 6 carbon atoms are methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl and *n*-pentyl.

Illustrative examples of pharmaceutically acceptable salts of the compounds of this invention include non-toxic acid addition salts formed with inorganic acids, such as, hydrochloric, hydrobromic, sulfuric and phosphoric acid, and organic acids, such as, methane sulfonic, salicylic, maleic, malonic, tartaric, citric and ascorbic acids; and non-toxic salts formed with inorganic or organic bases such as those of alkali metals, for example, sodium, potassium and lithium, alkaline earth metals, for example, calcium and magnesium, light metals of Group III A, for example, aluminum, organic amines, such as, primary, secondary or tertiary amines, for example, cyclohyxyl- amine, ethylamine, pyridine, methylamino- ethanol, ethanolamine and piperazine. The salts are prepared by conventional means.

Preferred compounds of this invention are those of general Formula I wherein R_1 is hydrogen or alkylcarbonyl wherein the alkyl moiety has from 1 to 4 carbon atoms and is straight or branched with compounds wherein R_1 is hydrogen being more preferred. Another preferred embodiment of this invention is the compounds of general Formula I wherein R_2 is hydroxy or a straight or branched alkoxy group of from 1 to 8 carbon atoms. Compounds wherein R_2 is hydroxy are more preferred. Compounds of general Formula I wherein each of R_3, R_4, R_5, R'_4 and R_6 is hydrogen or OR_{10} wherein R_{10} is hydrogen represent another preferred embodiment of this invention.

Illustrative examples of compounds of general Formula I are the following:
2-acetylene- 2-amino- 3-phenyl- propionic acid,
2-acetylene- 2-amino- 3-(3-hydroxyphenyl) propionic acid,
2-acetylene- 2-amino- 3(3,4-dihydroxy- phenyl) propionic acid.
2-acetylene- 2-amino- 3-(4-hydroxyphenyl) propionic acid,
2-acetylene- 2-amino- 3-(4-chloro- 2-hydroxyphenyl) propionic acid,
2-acetylene- 2-amino- 3-(4-chloro- 3-methoxyphenyl) propionic acid,
2-acetylene- 2-amino- 3-(2-chloro- 3-benzoyloxy- phenyl) propionic acid,
2-acetylene- 2-amino- 3-(2,4-dichloro- 3-hydroxyphenyl) propionic acid,
2-acetylene- 2-amino- 3-(2-chloro- 4-hydroxyphenyl) propionic acid,
2-acetylene- 2-amino- 3-(2-chloro- 6-methylphenyl) propionic acid,
2-acetylene- 2-amino- 3-(2,4-dichloro- 6-methylphenyl)- propionic acid,
2-acetylene- 2-amino- 3-(4-chloro- 6-methylphenyl) propionic acid,
2-acetylene- 2-amino- 3-(2-hydroxy- 4,6-dimethyl- phenyl)- propionic acid,
2-acetylene- 2-amino- 3-(2-chloro- 4,6-dimethyl- phenyl)- propionic acid,
2-acetylene- 2-amino- 3-(4-hydroxy- 6-methylphenyl) propionic acid,
2-acetylene- 2-amino- 3-(5-ethyl- 4-phenyl- propionyl- oxyphenyl)- propionic acid,
2-acetylene- 2-amino- 3-(4,6-diethyl- 2-hydroxyphenyl)- propionic acid,
2-acetylene- 2-amino- 3-(4-chloro- 6-ethylphenyl) propionic acid,
2-acetylene- 2-amino- 3-(4-chloro- 6-*tert*-butyl- phenyl)- propionic acid,
2-acetylene- 2-amino- 3-(6-*tert*-butyl- 4-hydroxyphenyl)- propionic acid,
2-acetylene- 2-(N-ethoxy- carbonylamino)- 3-(4-*n*-butoxy- phenyl)- propionic acid,
N,N-di-*n*-propyl 2-acetylene- 2-amino- 3-(4-acetyloxy- phenyl)- propionamide,
2-acetylene- 2-[N-(2-amino- 1-oxoethyl) amino]- 3-(3-hydroxyphenyl) propionic acid,
2-acetylene- 2-amino- 3-(3,4-dihydroxy) phenyl- 1-oxopropyl- aminoacetic acid,
2-[[2-acetylene- 2-amino- 1-oxo- 3-phenyl) propylamino) dihydrocinnamic acid,
2-acetylene- 2-(1-oxoethylamino)- 3-(4-hydroxy) phenyl- 1-oxopropylamino- 2-propionic acid,
methyl 2-acetylene- 2-(1-oxoethylamino)- 3-(4-hydroxy)- phenyl- 1-oxopropylamino- acetate,
2-acetylene- 2-amino- 3-phenylpropion- amide,
N,N-dimethyl 2-acetylene- 2-amino- 3-(3-hydroxyphenyl)- propionamide,
N,N-diethyl 2-acetylene- 2-amino- 3-(3',4'-dimethoxy- phenyl)- propionamide,
N-*n*-butyl 2-acetylene- 2-amino- 3-(4-hydroxyphenyl) propionamide,
methyl 2-acetylene- 2-amino- 3-(3-hydroxyphenyl) propionate, isopropyl 2-acetylene- 2-amino- 3-(3,4-dihydroxy- phenyl)- propionate,
tert-butyl 2-acetylene- 2-amino- 3-(4-hydroxy- phenyl) propionate, ethyl- 2-acetylene- 2-amino- 3(4-chloro- 3-methoxyphenyl)- propionate, and
2-acetylene- 2-amino- 3-(4-hydroxyphenyl) propionamide.

The compounds of general Formula 1 are irreversible inhibitors of the enzyme which metabolically catalyzes the conversion of tryptophan, 5-hydroxy- tryptophan, 3,4-dihyroxy- phenylalanine, tyrosine and phenylalanine to tryptamine, 5-hydroxy- tryptamine, 3,4-dihydroxy- phenyl- ethylamine, tyramine and phenethylamine respectively. As indicated hereinabove results of studies indicate that the enzyme responsible for the conversion of the above-enumerated amino acids to the respective amines peripherall is a non-specific aromatic amino acid decarboxylase. For central conversion studies indicate that specific decarboxylases are responsible for the conversion of each of 5-hydroxy- tryptophan and 3,4-dihydroxy- phenylalanine whereas the remaining above-enumerated amino acids are enzymatically transformed to the respect amines by a non-specific aromatic amino acid decarboxylase. The compounds of the present invention are effective in irreversibly inhibiting both centrally and peripherally the activity of non-specific aromatic amino acid decarboxylase as well as the activity of 3,4-dihyroxy- phenyl- alanine (DOPA) decarboxylase. As used herein with regard to the utility of the compounds of the present invention the term central refers to the central nervous system, primarily the brain, whereas peripheral refers to other body tissues wherein the decarboxylase enzyme is present. Selectivity of inhibition of the amino acid decarboxylases centrally or peripherally by administering compounds of general Formula I is dose dependent.

As irreversible inhibitors of aromatic amino acid decarboxylase, and DOPA decarboxylase the compounds of the present invention possess many pharmacologica utilities. As peripheral irreversible inhibitors of aromatic amino acid decarboxylase the compounds of general Formula I are useful in the treatment of Parkinsonism when given in conjunction with 3,4-dihydroxy- phenyl- alanine (DOPA) or L-3,4-dihydroxy- phenyl- alanine (L-DOPA). DOPA and more particularly the active isomer L-DOPA are known to be effective in treating Parkinsonism when administered systemically, usually in an amount from 0.5 to 1 gram daily

initially after which the amount administered is gradually increased over a 3 to 7 day period to a maximally tolerated daily dose of about 8 grams. Concurrent administration of a compound of general Formula I and L-DOPA provides an improved method of treating Parkinsonism in that the compounds of Formula I will block the decarboxylation of L-DOPA to L-3,4-dihydroxy- phenethyl- amine (L-dopamine) peripherally by inhibiting the activity of aromatic amino acid decarboxylase enzyme, thus retaining high circulating levels of L-DOPA for central absorption and also preventing peripheral formation of increased levels of dopamine which is known to result in certain undesirable side effects such as cardiac arrhythmia. By concurrently administering a compound of general Formula I and L-DOPA the amount of L-DOPA administered may be reduced 2 to 10-fold as compared to amounts required for utility when L-DOPA is administered alone. It is preferred that the compounds of this invention be administered prior to administration of L-DOPA. For example, a compound of Formula I may be administered from 30 minutes to 4 hours prior to administration of L-DOPA depending on the route of administration and condition of the patient to be treated.

The compounds of general Formula I are also useful in treating depressive syndromes in individuals when given in conjunction with 5-hydroxy- tryptophan (5-HTP) or more particularly the active levo isomer which is known to be useful in the treatment of depression when administered systemically. The compounds of general Formula I, by inhibiting peripherally the activity of aromatic amino acid decarboxylase will block the conversion of 5-hydroxy- tryptophan to 5-hydroxy- tryptamine thus retaining higher circulating levels of 5-HTP for central absorption. The compounds of general Formula I when administered concurrently with exogenous 5-HTP are also useful in treating action myoclonus which is known to be effectively treated by increasing central levels of 5-HTP.

The compounds of general Formula I, by virtue of their inhibitory action on aromatic amino acid decarboxylase peripherally are also useful in the treatment of rheumatoid arthritis, carcinoid syndrome, anaphylactoid reactions in humans, bronchoconstriction in asthamatic humans as well as other conditions known to be caused by high peripheral levels of 5-hydroxy- tryptamine.

As indicated hereinabove it has been shown that agents which decrease the elevated levels of 5--HT and norepinephrine, the hydroxylation product of dopamine, are useful in treating patients with manic disorders. Hence, as central irreversible inhibitors of aromatic amino acid decarboxylase, and DOPA decarboxylase the compounds of general Formula I are useful in treating manic disorders. Additionally, by virtue of the central inhibitory action of the compounds of general Formula I on aromatic amino acid decarboxylase said compounds may also be useful as antipsychotic agents, since central levels of tryptamine are decreased, and useful in the treatment of schizophrenia and seizure disorders since central levels of phenethylamine and tyramine are decreased by administration of a compound of general Formula I.

The utility of the compounds of general Formula I as irreversible inhibitors of aromatic amino acid decarboxylase may be demonstrated as follows. A compound of general Formula I is administered as an aqueous solution or suspension to rats or mice. At difference time intervals after administration of the compound from 1 to 48 hours the animals are sacrificed by decapitation and aromatic amino acid decarboxylase activity is measured by a radiometric assay as described by Christenson et al., Arch. Biochem. Biophys. *141*, 356 (1970) in homogenates of kidney, heart and brain prepared according to Burkard et al., Arch. Biochem. Biophys. *107*, 187 (1964).

The compounds of this invention can be administered in various manners to achieve the desired effect. The compounds can be administered alone or in the form of pharmaceutical preparations to the patient being treated either orally or parenterally, for example, subcutaneously, intravenously or intraperitoneally. The compounds can be administered by intranasal instillation or by application to mucous membranes such as that of the nose, throat and bronchial tubes, for example, in an aerosol spray containing small particles of a novel compound of this invention in a spray solution or dry powder form.

The amount of novel compound administered will vary and can be any effective amount. Depending on the patient, the condition being treated and the mode of administration, the quantity of novel compound administered may vary over a wide range to provide an effective amount in a unit dosage form. When the compounds of general Formula I are administered to affact a peripheral irreversible inhibition or aromatic decarboxylase the effective amount of compound administered will vary from about 01. mg/kg (milligrams per kilogram) to 100 mg/kg of body weight of the patient per dose and preferably from about 5 mg/kg to 25 mg/kg. For example, the desired peripheral effect can be obtained by consumption of a unit dosage form, such as, for example, a tablet containing from 10 to 250 mg of a novel compound of this invention taken 1 to 4 times daily. When the compounds of general Formula I are administered to achieve a central irreversible inhibition of aromatic decarboxylase or 3,4-dihydroxy- phenylal- anine decarboxylase the effective amount of compound administered will vary from about 100 mg/kg to 500 mg/kg of body weight of the patient per day and preferably from about 150 mg/kg to 300 mg/kg. For example, the desired central effect can be achieved by consumption of a unit dosage form, such as, for example, a tablet containing from about 350 mg to 500 mg of a novel compound of this invention taken from 1 to 4 times daily.

As used herein the term patient is taken to mean warm blooded animals such as mammals, for example, cats, dogs, rats, mice, guinea pigs, sheep, horses, bovine cows, and humans.

The solid unit dosage forms can be of the conventional type. Thus, the solid form can be a capsule which can be of the ordinary gelatin type containing a novel compound of this invention and a carrier, for example, lubricant and inert fillers such as lactose, sucrose and corn starch. In another embodiment, the novel compounds are tableted with conventional tablet bases such as lactose, sucrose or corn starch in combina-

tion with binders such as acacia, corn starch or gelatin, disintegrating agents such as corn starch, potato starch, or alginic acid, and a lubricant such as stearic acid, or magnesium stearate.

For parenteral administration the compounds may be administered as injectable dosages of a solution or suspension of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid such as water and oils with or without the addition of a surfactant and other pharmaceutically acceptable adjuvants. Illustrative of oils which can be employed in these preparations are those of petroleum, animal, vegetable or synthetic origin, for example, peanut oil, soybean oil, and mineral oil. In general water, saline, aqeous dextrose, and related sugar solutions, ethanols and glycols such as propylene glycol or polyethylene glycol are preferred liquid carriers, particularly for injectable solutions.

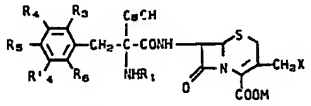
The compounds can be administered in the form of a depot injection or implant preparation which may be formulated in such a manner as to permit a sustained release of the active ingredient. The active ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or intramuscularly as depot injections or implants. Implants may employ inert materals such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber manufactured by the Dow-Corning Corporation.

For use as aerosols the novel compounds in solution or suspension may be packaged in a pressurized aerosol container together with a gaseous or liquified propellant, for example, dichloro- difluoro- methane, dichloro- difluoro- methane with dichloro- difluoro- ethane, carbon dioxide, nitrogen or propane, with the usual adjuvants such as cosolvents, and wetting agents, as may be necessary or desirable. The compounds may also be administered in a non-pressurized from such as in a nebulizer or atomizer.

As indicated hereinabove the compounds of general Formula I find particular utility when administered together with exogenous L-DOPA in which case individual formulations of a compound of general Formula I and L-DOPA may be administered, or both active ingredients may be formulated into a single combination pharmaceutical formulation. In either mode of administration the amount of compound of general Formula I as compared to the amount of L-DOPA administered will vary from about 1:1 to 1:10. A combination formulation may contain an internal portion containing L-DOPA and an outer portion containing a compound of general Formula I, each active ingredient being suitably formulated. A particularly suitable combination formulation may be prepared by compressing L-DOPA, optionally with suitable carriers, to a core, providing said core with a laminated coating that is resistant to gastric juice, and applying over the coated core an external layer that contains a compound of general Formula I suitably formulated. Using such a combination formulation the decarboxylase inhibitor, that is, a compound of General Formula I is released, preferably 30 to 60 minutes prior to the L-DOPA. The laminated coating may be formed by use of a nonaqueous solution of glycerides or a water-insoluble polymer such as ethyl cellulose or cellulose acetate phthalate. Formulation wherein the L-DOPA is enteric coated by use of mixtures of shellacs and shellac derivaties and cellulose acetate phthalates may also be employed.

In the specific examples included hereinbelow illustrative examples of suitable pharmaceutical formulations are described.

In addition to beign useful pharmacological agents compounds of general Formula I are also useful as intermediates for the preparation of useful cephlosporin antibiotics. Compounds of general Formula I wherein R_2 is hydroxy are useful in the preparation of cephalosporin derivatives of the following general Formula II:



Formula II

In the above general Formula II, R_1, R_3, R_4, R_5, R'_4 and R_6 have the meanings defined in general Formula I; M is hydrogen or a negative charge; and X is hydrogen or acetoxy.

The compounds of general Formula II and the pharmaceutically acceptable salts and individual optical isomers thereof are novel compounds useful as antibiotics and can be administered in a manner similar to that of many well known cephalosporin derivatives, for example, cephalexin, cephalothin, or cephaloglycine. The compounds of general Formula II and pharmaceutically acceptable salts and isomers thereof can be administered alone or in the form of pharmaceutical preparations either orally or parenterally and topically to warm blooded animals, that is, birds and mammals, for example, cats, dogs, bovine cows, sheep, horses and humans. For oral administration the compounds can be administered in the form of tablets, capsules or pills or in the form of elixirs or suspensions. For parenteral administration, the compounds may best be used in the form of a sterile aqueous solution which may contain other solutes, for example, enough saline or glucose to make the solution isotonic. For topical administration the compounds of general Formula II, salts and isomers thereof may be incorporated into creams or ointments.

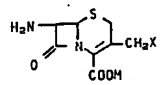
Illustrative examples of bacteria against which the compounds of general Formula II and the pharmaceutically acceptable salts and individual optical isomers thereof are active are *Staphylococcus aureus*, *Salmonella schotmuehleri*, *Klebsiella pneumoniae*, *Diplococcus pneumoniae* and *Streptococcus pyogenes*.

Illustrative pharmaceutically acceptable non-toxic inorganic acid additions salts of the compounds of general Formula II are mineral acid addition salts, for example, hydrogen chloride, hydrogen bromide, sulfates, sulfamates, phosphate, and organic acid addition salts are, for example, maleate, acetate, citrate,

oxalate, succinate, benzoate, tartrate, fumarate, malate and ascorbate. The salts can be formed by conventional means.

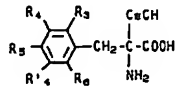
Illustrative examples of cephalosporin derivatives as represented by general Formula II are 7-[[2-acetylene-2-amino- 3-phenyl- propionyl]amino]- 3-acetyloxymethyl- 8-oxo-5-thia- 1-azabicyclo[4.2.0]oct- 2-ene-2-carboxylic acid, 7-[[2-acetylene- 2-amino- 3-(3-hydroxyphenyl) propionyl]-amino]- 3-acetyloxy- methyl-8-oxo-5-thia- 1-azabicyclo[4.2.0]-oct-2-ene- 2-carboxylic acid, 7-[[2-acetylene- 2-amino- 3-(3,4-dihydroxy-phenyl) propionyl]amino]- 3-acetyloxy- methyl- 8-oxo-5-thia- 1-azabicyclo[4.2.0]oct- 2-ene-2-carboxylic acid, and 7-[[2-acetylene- 2-amino- 3-(4-hydroxyphenyl)- propionyl]amino]- 3-acetyloxymethyl- 8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-ene- 2-carboxylic acid.

The compounds of general Formula II wherein R_1 is hydrogen are prepared by coupling 7-aminocephalosporanic acid or a derivative thereof having the formula



Formula III

wherein X and M have the meanings defined in general Formula II with an acid of the formula



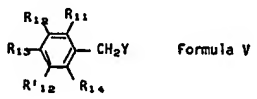
Formula IV

or a functional derivative thereof such as the acid chloride or an acid anhydride and in the presence of a dehydrating agent such as dicyclohexyl- carbodiimide, when the free acid is used, wherein R_3, R_4, R_5, R'_4, and R_6 have the meanings defined in general Formula II and the amino group is protected with a suitable blocking group such as *tert*butoxy- carbonyl followed by acid hydrolysis to remove the amino protecting groups.

The coupling reaction is generally carried out in a solvent, such as, ethyl acetate, dioxane, chloroform or tetrahydro- furan in the presence of a base, such as, alkaline bicarbonate. The temperature of the reaction time may vary from about 1/2 hour to 10 hours. The cephalosporin products are isolated by conventional procedures. The compounds of general Formula IV are prepared by procedures described hereinabove and the compounds of Formula III are commercially available or are made by procedures well known in the art.

The compounds of general Formula II wherein R_1 is other than hydrogen are prepared from the corresponding derivaties wherein R_1 is hydrogen by the general procedures set forth hereinbelow for compounds of general Formula I wherein R_1 is other than hydrogen.

The compounds of general Formula I wherein R_2 is hydroxy, R_1 is hydrogen and both R_3 and R_4 are OR_{10} wherein R_{10} is hydrogen or both R_4 and R_5 are OR_{10} wherein R_{10} is hydrogen, btoh R_4 and R_5 together are $-O-CH_2-O-$, or wherein each or R_3, R_4, R_5, R'_4 and R_6 has the meanings defined in Table I except R_{10} is methyl are prepared by treating a suitably protected propargylamine derivative with a strong base to form a protected propargylamine carbanion intermediate which is alkylated respectively when R_3 and R_4 are both OR_{10} and R_{10} is hydrogen with 2,3-isopropylidene- dioxybenzyl- halide and, when R_4 and R_5 are both OR_{10} and R_{10} is hydrogen, with 3,4-isopropylidene- dioxybenzyl- halide, and when R_4 and R_5 together are $-O-CH_2-O-$ with 3,4-methylene- dioxybenzyl- halide wherein halide is, for example, chloride or bromide, and, when R_3 to R_6 and R'_4 are otherwise described above, with a compound of the formula:



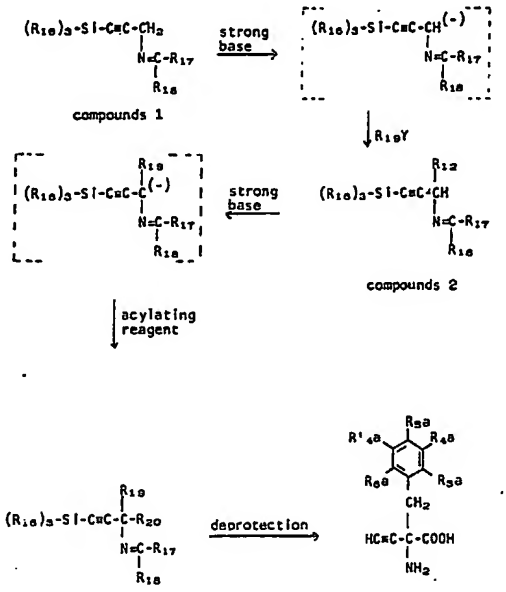
Formula V

wherein Y is a halogen atom, for example, chlorine or bromine and each or R_{11}, R_{12}, R_{13}, R'_{12} and R_{14} has the meanings defined in the following Table II wherein R_{15} is methyl:

TABLE II

R_{11}	R_{12}	R_{13}	R'_{12}	R_{14}
H	H	H	H	H
H	H	OR_{15}	H	H
H	OR_{15}	H	H	H
H	OR_{15}	OR_{15}	H	H
OR_{15}	H	Cl	H	H
H	OR_{15}	Cl	H	H
Cl	OR_{15}	H	H	H
Cl	OR_{15}	Cl	H	H
Cl, F	H	OR_{15}	H	H
Cl	H	H	H	CH_3
Cl	H	Cl	H	CH_3
H	H	Cl, F	H	CH_3
OR_{15}	H	CH_3	H	CH_3
Cl	H	CH_3	H	CH_3
H	H	OR_{15}	H	CH_3
H	H	OR_{15}	H	C_2H_5
OR_{15}	H	C_2H_5	H	C_2H_5
H	OR_{15}	H	OR_{15}	H
H	OR_{15}	OR_{15}	OR_{15}	H
H	H	OCH_3	OCH_2Ph	H
H	H	OCH_2Ph	OCH_3	H
OR_{15}	OR_{15}	H	H	H
OR_{15}	H	H	H	H
H	H	Cl	H	C_2H_5
H	H	Cl	H	tert-C_4H_9
H	H	OR_{15}	H	tert-C_4H_9

The thus formed alkylated propargylamine derivative is treated with a strong base to form an alkylated propargylamine carbanion, said second carbanion intermediate is treated with an acylating reagent with subsequent removal of the protecting groups as represented by the following reaction sequence:



In the above reaction scheme R_{16} represents a straight or branched lower alkyl group having from 1 to 4 carbon atoms, such as, methyl, ethyl, *n*-propyl and *tert*-butyl; R_{17} is phenyl, *tert*-butyl or triethyl- methyl, 1-adamantanyl or 2-furyl; R_{18} is hydrogen, methoxy or ethoxy with the proviso that when R_{17} is 1-adamantanyl or 2-furyl, R_{18} is not hydrogen; $R_{19}Y$ represents the alkylating reagents of Formula V or 2,3-isopropylidene- dioxybenzyl- halide, 3,4-isopropylidene- dioxybenzyl- halide or 3,4-methylene-

dioxybenzyl- halide; Ph represents phenyl; R_{20} is a carboxy anion, a carboxylic acid ester, a carboxamide, a nitrile or other group capable of being hydrolyzed to a carboxylic acid function which varies with the acylating reagent employed; and each of R_{3a}, R_{4a}, R_{5a}, R'_{4a} and R_{6a} respectively has the meaning defined for R_3, R_4, R_5, R'_4 and R_6 in Table I except R_{10} is methyl, or both or R_{3a} and R_{4a} are OR_{10} and R_{10} is hydrogen, or both R_{4a} and R_{5a} represent OR_{10} wherein R_{10} is hydrogen.

Suitable strong bases which may be employed in the above reaction to form each carbanion are those which will abstract a proton from the carbon atom adjacent to the acetylene moiety, such as, alkyl lithium, for example, butyl lithium or phenyl lithium, lithium di-alkylamide, for example, lithium diisopropylamide, lithium amide, tertiary potassium butylate or sodium amide.

The alkylating reagents employed in the above reaction sequence are known in the art or can be prepared by procedures known in the art. For example, 2,3-isopropylidene- dioxy benzyl halide may be obtained from 2,3-dihydroxy- toluene by treatment with acetone in the presence of phosphorus pentoxide followed by treatment with bromosuccinimide by the general procedure of K. Ogura and G. Tsuchihashi, Tetrahedron Letters *1971*, 3151.

Suitable acylating reagents which may be employed in the above reaction are halo-formates, such as chloromethyl formate or chloro ethylformate, azido *tert*-butyl- formate, cyanogen bromide, carbon dioxide, diethyl- carbonate, phenylisocyanate, triethoxy- methylium tetrafluoro- borate, N,N-dimethyl- carbamoyl chloride, 2-methylthio- 1,3-dithiolinium iodide, ethylene carbonate or ethylene trithio- carbonate. When 2-methylthio- 1,3-dithiolinium iodide is employed the additional step of alcoholysis with a lower alcohol, for example ethanol or isopropyl alcohol is required prior to deprotection by hydrolysis.

The alkylating reaction and the acylating reaction may be carried out in an aprotic solvent, for example, benzene, toluene, ethers, tetrahydrofuran, dimethyl- sulfoxide, hexamethyl phosphor- triamide. For each reaction the temperature varies from −120°C to about 25°C, a preferred reaction temperature being about −70°C, and the reaction time varies from about 1/2 hour to 24 hours.

Removal of the protecting groups is achieved by treatment with aqueous base, for example, sodium or potassium hydroxide or use of hydrazine or phenyl- hydrazine followed by acid hydrolysis with, for example, hydrochloric acid when the alkylating reagent is 3,4-isopropylidene- dioxybenzyl halide or 2,3-isopropylidene- dioxybenzyl halide, and when the alkylating reagent contains a benzyloxy group base hydrolysis is followed by treatment with lithium amide or sodium amide in ammonia followed by the addition of lithium or sodium metal until the blue color persists for about 15 minutes.

The propargylamine derivatives wherein R_{18} is hydrogen are prepared by the addition of protecting groups on the acetylene function and the nitrogen function of propargylamine. Protection of the nitrogen function of the propargylamine is accomplished by forming in a known manner a Schiff's base with a nonenolizable carbonyl bearing compound selected from benzaldehyde, 2,2-dimethyl- propanal and 2,2-diethyl- butanal. Protection of the acetylenic function is accomplished by reacting the above-described Schiff's base with a trialkyl- silylchloride wherein the alkyl moiety has from 1 to 4 carbon atoms and is straight or branched, for example, trimethyl- silylchloride or triethyl- silylchloride forming in a known manner the corresponding trialkyl- silyl derivative.

The propargylamine derivatives wherein R_{18} is methoxy or ethoxy are prepared by reacting propargylamine wherein the acetylene function is protected by a trialkylsilyl group, wherein the alkyl moiety has from 1 to 4 carbon atoms, with benzoyl chloride, pivalic acid chloride, 2,2-diethyl- butyric acid chloride, 2-furoic acid chloride or 1-adamantane carboxylic acid chloride at 0°C in diethyl ether, dioxane, tetrahydrofuran, chloroform, methylene- chloride, dimethyl- formamide, dimethyl- acetamide, or chloro- benzene in the presence of an organic base such as triethylamine or pyridine after which the reaction mixture is allowed to warm to about 25°C for one hour. The resulting amide derivative is combined with an alkylating reagent, such as, methyl- fluoro- sulfonate, dimethyl- sulfate, methyliodide, methyl *p*-toluene- sulfonate or trimethyloxonium hexafluoro- borate when R_{18} is methoxy and triethyloxonium tetrafluoro- borate when R_{18} is ethoxy at about 25°C in a chlorinated hydrocarbon solvent such as methylene chloride, chlorobenzene or chloroform, and the reaction mixture is then cooled to about 25°C and an organic base such as triethylamine or pyridine is added, after which the solution is extracted with brine and the product isolated.

The protected propargylamine starting material is obtained by treating a 3-trialkyl- silylprop- 2-ynyl- 1-iminobenzyl derivative with hydrazine or phenyl- hydrazine at about 25°C for about 1/2 hour after which the mixture is diluted with, for example, petroleum ether, benzene or toluene and the protected propargylamine derivative isolated. Alternatively treatment with 0.5 to 1 N HCl gives the hydrochloride.

The compounds of general Formula V are known in the art or may be prepared from the corresponding appropriately substituted benzoic acid or benzaldehyde derivatives which are known in the art. For example, the benzylhalides of Formula V may be prepared from the corresponding benzaldehyde by reduction with sodium borohydride, lithium aluminum hydride or by catalytic reduction or from the corresponding benzoic acid ester by reduction with lithium aluminum hydride or borane or reduction of the corresponding benzoic acid derivative with lithium hydride and treating the thus formed benzyl alcohol derivative with, for example, thionyl chloride, phosphorus oxychloride, phosphorus trichloride, phosphorus tribromide or phosphorus pentachloride.

The compounds of general Formula I wherein R_1 is hydrogen, R_2 is hydroxy and either of R_3, R_4, R_5 or R'_4 is OR_{10} wherein R_{10} is hydrogen are prepared from the corresponding derivative wherein either of R_3, R_4, R_5 or R'_4 is OR_{10} and R_{10} is methyl by treatment of said derivative with a lower alcohol, such as, methanol saturated

with anhydrous HCl for about 15 hours at about 25°C to form the lower alkyl ester, for example, the methyl ester which is suspended in methylene chloride, dimethyl- formamide, dimethyl- acetamide, chloro- benzene or an ether such as diethyl ether, dioxane or tetrahydro- furan and treated with benzoyl chloride followed by treatment with an organic base such as triethylamine or pyridine with stirring for about 24 hours at about 25°C to give the lower alkyl ester derivative wherein the amino group is protected with phenylcarbonyl which is subsequently treated with a Lewis acid, such as, boron tribromide, boron trichloride or boron trifluoride then as aqueous acid, for example, hydrochloric acid.

Compounds of general Formula I wherein R_1 is hydrogen, R_2 is hydroxy and any of R_3, R_4, R_5 or R'_4 is OR_{10} and R_{10} is a straight or branched alkyl group of from 1 to 8 carbon atoms may be prepared by alkylating the corresponding compounds wherein R_{10} is hydrogen with an alkyl halide of the formula $R_{21}Y_2$ wherein R_{21} is a straight or branched alkyl group of from 1 to 8 carbon atoms and Y_2 is halogen, for example, bromine or iodine in a lower alcoholic solvent such as methanol or ethanol or hydrocarbon solvents such as benzene or toluene in the presence of an organic base such as triethylamine or pyridine or in an aprotic solvent such as dimethyl- formamide, dimethyl- acetamide or dimethyl- sulfoxide in the presence of sodium hydride for about 1 to 24 hours at a temperature of about 25°C to 85°C followed by hydrolysis with aqueous base with the proviso that prior to the alkylation reaction the α-amino group of the hydroxy substituted starting material is protected with a suitable protecting group such as *tert*-butoxycarbonyl which is subsequently removed by treatment with acid, such as, trifluoro- acetic acid. The alkyl halides employed in the above reaction are known in the art or can be prepared by procedures well known in the art.

The compounds of general Formula I wherein R_2 is hydroxy or a straight or branched alkoxy group of from 1 to 8 carbon atoms, R_1 is hydrogen and any of R_3, R_4, R_5 or R'_4 is OR_{10} and R_{10} is alkylcarbonyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched, benzoyl, or phenyl- alkylene- carbonyl wherein the alkylene moiety is straight or branched and has from 1 to 6 carbon atoms are prepared by treating the corresponding derivatives wherein R_{10} is hydrogen with an acid anhydride of the formula

$$(R_{22}-\overset{\overset{O}{\|}}{C}-)_2O$$ or an acid halide of the formula $$R_{22}-\overset{\overset{O}{\|}}{C}-\text{halo}$$

wherein halo is chlorine or bromine and R_{22} is a straight or branched alkyl group of from 1 to 6 carbon atoms, phenyl or phenyl- alkylene wherein the alkylene moiety is straight or branched and has from 1 to 6 carbon atoms in the presence of an organic base aushc as pyridine, quinoline or triethylamine, which base serves as the solvent, for about 1 to 24 hours at a temperature of about 25°C to 100°C with the proviso that prior to the reaction the α-amino group of the hydroxy substituted starting material is protected with a suitable blocking group, such as, *tert*-butoxy- carbonyl which is subsequently removed by treatment with acid, for example, trifluoro- acetic acid.

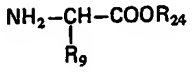
The acid anhydride and acid halide reactants employed in the above reaction are known in the art or can be prepared from the appropriate acids by procedures well known in the art.

The compounds of general Formula I wherein R_2 is a straight or branched alkoxy group of from 1 to 8 carbon atoms are prepared by treating the corresponding derivatives wherein R_2 is hydroxy with thionyl chloride to form the acid chloride which is reacted with an alcohol of the formula R_{23}–OH, wherein R_{23} is a straight or branched alkyl group of from 1 to 8 carbon atoms, such as, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, hexyl, or octyl, at about 25°C for from about 4 to 12 hours.

The compounds of general Formula I wherein R_2 is $-NR_7R_8$ wherein each of R_7 and R_8 is hydrogen or a straight or branched lower alkyl of 1 to 4 carbon atoms are prepared by an acylation reaction of an acid halide, for example, an acid chloride, or the corresponding compound wherein R_2 is hydroxy and R_1 has the meaning defined in Formula I with the proviso that any free amino group is protected with a suitable protecting group, for example, carbobenzyloxy or *tert*-butoxy- carbonyl and when any of R_3, R_4, R_5 or R'_4 is OR_{10} and R_{10} is hydrogen said groups are protected as the corresponding alkylcarbonyloxy group, with an excess of an appropriate amine which may be represented as NHR_7R_8. The reaction is carried out in methylene chloride, chloroform, dimethyl- formamide, ethers such as tetrahydro- furan or dioxane or benzene at about 25°C for about 1 to 4 hours. Suitable amines are, for example, ammonia, or a compound which is a potential source of ammonia, for example, hexamethylene- tetramine; primary amines, for example, methylamine, theylamine, or *n*-propylamine; and secondary amines such as dimethylamine, diethylamine or di-*n*-butylamine. Following the acylation reaction the amino protecting group is removed by treatment with acid or hydrogen bromide in dioxane, and the hydroxy protecting group when appropriate is removed by base or acid hydrolysis.

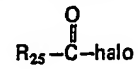
The compounds of general Formula I wherein R_2 is $$-NH-\underset{\underset{R_9}{|}}{CH}-COOH$$

are prepared by reacting the corresponding derivative wherein R_2 is hydroxy or a functional derivative thereof such as an acid anhydride and R_1 has the meaning defined in Formula I with the proviso that any free amino group is protected with a suitable blocking group, such as benzyloxy- carbonyl or *tert*-butoxy- carbonyl with a compound of the formula

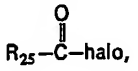


wherein R_9 has the meaning defined in general Formula I and R_{24} is a lower alkyl group, for example, methyl or ethyl in an ether, such as, tetrahydrofuran or dioxane at 0° to about 50°C for about 1 to 24 hours followed by acid hydrolysis to remove the protecring group, with the proviso that when the amine protected free acid is employed the reaction is carried out using a dehydrating agent such as dicyclohexyl- carbodiimide.

The compounds of general Formula I wherein R_1 is alkylcarbonyl wherein the alkyl moiety is straight or branched and has from 1 to 4 carbon atoms are prepared by treating the corresponding derivatives wherein R_1 is hydrogen and R_2 is hydroxy with an acid halide of the formula

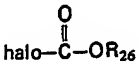


wherein halo is a halogen atom, for example, chlorine or bromine and R_{25} is a straight or branched alkyl group having from 1 to 4 carbon atoms in water in the presence of a base such as sodium hydroxide or sodium borate at a temperature of from 0°C to 25°C for from 1/2 hour to 6 hours. These compounds may also be prepared from the ester derivative, that is, compounds of general Formula I wherein R_1 is hydrogen and R_2 is an alkoxy group of from 1 to 8 carbon atoms by treatment with the acid halide,



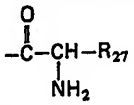
described above, in water, methylene chloride, chloroform or dimethyl acetamide in the presence of a base such as sodium hydroxide, potassium hydroxide or excess triethyl- amine at a temperature of from about 0°C to 25°C for from about 1/2 hour to 24 hours.

The compounds of general Formula I wherein R_1 is alkoxy carbonyl wherein the alkoxy moiety is straight or branched and has from 1 to 4 carbon atoms are prepared by treating the corresponding derivative wherein R_1 is hydrogen and R_2 is hydroxy with an alkyl haloformate of the formula

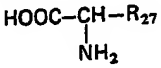


wherein halo is a halogen atom such as chlorine or bromine and R_{26} is a straight or branched alkyl group having from 1 to 4 carbon atoms in water in the presence of a base such as sodium hydroxide or sodium borate at a temperature of from about 0°C to 25°C for from about 1/2 hour to 6 hours.

The compounds of general Formula I wherein R_1 is



wherein R_{27} is hydrogen, a straight or branched lower alkyl group of from 1 to 4 carbon atoms, benzyl or *p*-hydroxybenzyl are prepared by treating the corresponding derivative wherein R_1 is hydrogen and R_2 is a straight or branched alkoxy group of from 1 to 8 carbon atoms with an acid of the formula



or an anhydride thereof wherein the amino group is protected with a suitable blocking group such as benzyloxy- carbonyl or *tert*-butoxy- carbonyl and R_{27} has the maning defined hereinabove in an ether, such as, tetrahydro- furan or dioxane, methylene chloride or chloroform and in the presence of a dehydrating agent when the free acid is employed, at a temperature of from about 0°C to 35°C for about 1 to 12 hours followed by acid and base hydrolysis to remove the protecting groups.

The individual optical isomers of the compounds of general Formula I wherein R_1 is H and R_2 is OH may be separated by using a (+) of (−) binaphthyl- phosphoric acid salt by the method of R. Viterbo et al., Tetrahedron Letters *48*, 4617 (1971). Other resolving agents such as (+) camphor-10- sulfonic acid may also be employed. The individual optical isomers of compounds of Formula I wherein R_1 and R_2 are other than H and OH may be obtained as described herein for the racemate only starting with the resolved amino acid.

The following Example 1 illustrates the use of a compound of general Formula I wherein R_2 is hydroxy as a chemical intermediate in the preparation of a cephalosporin of Formula II.

EXAMPLE 1

7[[2-Acetylene- 2-amino- 3-phenyl- propionyl]amino]- 3-acetyl- oxymethyl- 8-oxo- 5-thia-1-azabicyclo[4.2.0]oct- 2-ene-2-carboxylic acid

A mixture of 1 g of 3-acetyloxy- 7- amino- 8-oxo- 5-thia-1-azabicyclo[4.2.0]oct-2-ene- 2-carboxylic acid and 1 g of 2-acetylene- 2-amino- 3-phenyl- propionic acid chloride wherein the free amino group is protected with *tert*-butoxy- carbonyl in 50 ml of ethyl acetate is refluxed for 2 hours after which the solvent is removed leaving a residue which is treated with mild acid and chromatographed on silica gel using benzene-acetone as the eluant to give 7-[[2-acetylene- 2-amino- 3-phenyl- propionyl]amino]- 3-acetyloxy- methyl- 8-oxo-5-thia-

1-azabicyclo[4.2.0]oct- 2-ene-2-carboxylic acid.

The following Examples 2 to 4 are illustrative of pharmaceutical preparations of the compounds of this invention.

EXAMPLE 2

An illustrative composition for hard gelatin capsules is as follows:

(a)	2-acetylene-2-amino-3-(3-hydroxy-phenyl)propionic acid	20 mg
(b)	talc	5 mg
(c)	lactose	90 mg

The formulation is prepared by passing the dry powders of (a) and (b) through a fine mesh screen and mixing them well. The powder is then filled into hard gelatin capsules at a net fill of 115 mg per capsule.

EXAMPLE 3

An illustrative composition for tablets is as follows:

(a)	2-acetylene-2-amino-3-(3,4-dihydroxyphenyl)propionic acid	20 mg
(b)	starch	43 mg
(c)	lactose	45 mg
(d)	magnesium stearate	2 mg

The granulation obtained upon mixing the lactose with the compound (a) and part of the starch and granulated with starch paste is dried, screened, and mixed with the magnesium stearate. The mixture is compressed into tablets weighing 110 mg each.

EXAMPLE 4

An illustrative composition for an injectable suspension is the following 1 ml ampul for an intramuscular injection.

		Weight per cent
(a)	2-acetylene-2-amino-3-(4-hydroxyphenyl)propionic acid	1.0
(b)	polyvinylpyrrolidone	0.5
(c)	lecithin	0.25
(d)	water for injection to make	100.0

The materials (a)–(d) are mixed, homogenized, and filled into 1 ml ampuls which are sealed and autoclaved 20 minutes at 121°C. Each ampul contains 10 mg per ml of novel compound (a).

The following Examples further illustrate the compounds of general Formula I.

EXAMPLE 5

2-Acetylene- 2-amino- 3-(3,4-dihydroxy- phenyl) propionic acid

(A) A solution of 32.4 g (0.15 M) of 3-trimethyl- silylprop- 2-ynyl-1- iminobenzyl in 20 ml of tetrahydro- furan is added to lithium diisopropylamide, prepared from 21 ml (0.15 M) of diisopropylamide and 73.2 ml of a 2.05 M solution of *n*-butyllithium (0.15 M), in 1 liter of tetrahydro- furan at −78°C. After 15 minutes 32.7 g (1.35 M) of 3,4-isopropylidene- dioxybenzyl- bromide in 20 ml of tetrahydro- furan is added, and the mixture is maintained at −78°C for 2 hours after which 73.2 ml of a 2.05 M solution (0.15 M) of *n*-butyllithium is added followed by the addition of 14.2 g, 11.6 ml (0.15 M) of methyl chloroformate. After an additional 30 minutes at −78°C the reaction mixture is treated with brine and extracted with ether. The ether extract is evaporated leaving a residue which is dissolved in 300 ml of petroleum ether, b.p. 30°–60°C, and treated with 16.2 g (0.15 M) of phenyl- hydrazine at 25°C for 2 hours. The precipitate is filtered off and the petroleum ether evaporated leaving a residue which is treated with 40 g of potassium hydroxide in 300 ml of ethanol and 300 ml of water at 25°C for about 15 hours. The ethanol is evaporated, and the aqueous solution is washed well with methylene chloride, then acidified and rewashed with methylene chloride. The water is evaporated, and the remaining solid residue is triturated with ethanol, filtered and the filtrate evaporated leaving a residue which

is dissolved in water. The pH of the water solution is adjusted to 6 and applied to a column of Amberlite resin 120 H^+ and eluting with 2 M ammonium hydroxide solution affords 2-acetylene- 2-amino- 3',4'œ isopropylidene- dioxyphenyl- propionic acid after recrystallization from water-ethanol.

(B) 3 g (0.13 M) of 2-acetylene- 2-amino- 3,4-isopropylidene- dioxyphenyl- propionic acid is heated at reflux with 200 ml of 6 N hydrochloric acid for 2 hours after which the solvent is evaporated. The resulting residue is taken up in water and the pH is adjusted to 6 by careful addition of hydrazine hydrate. On cooling the solution to 0°C a precipitate forms which is collected and recrystallized (charcoal) from water to afford 2-acetylene- 2-amino- 3-(3,4-dihydroxy- phenyl) propionic acid.

EXAMPLE 2

2-Acetylene- 2-amino- 3-(3-methoxy- phenyl) propionic acid

When in the procedure of Example 5 (A) 25.8 g (0.12 M) of 3-trimethyl- silylprop- 2-ynyl-1- iminobenzyl is used instead of 32.4 g (0.15 M) and 20.1 g (0.1 M) of 1-bromomethyl- 3-methoxy- benzene is used in place of 5-bromomethyl- 1,3-benzoidioxole, upon recrystallization from water, 2-acetylene- 2-amino- 3-(3-methoxy- phenyl) propionic acid is obtained.

EXAMPLE 7

2-Acetylene- 2-amino- 3-(3-hydroxy- phenyl) propionic acid

A suspension of 2.0 g (9.1 mM) of 2-acetylene- 2-amino- 3-(3-methoxy- phenyl) propionic acid in 20 ml of methanol saturated with anhydrous HC1 is stirred for about 15 hours at 25°C after which the solvent is evaporated. The resulting methyl ester derivative is suspended in 50 ml of methylene chloride and treated with 1.26 g of benzoyl chloride followed by treatment with 3.6 g of triethylamine. The mixture is stirred for 24 hours then washed with water, dried and evaporated. The resulting residue is recrystallized from methanol to give the methyl ester derivative wherein the amino group is protected with phenyl- carbonyl.

A solution of 1.2 g (3.5 mM) of the amine protected methyl ester in 50 ml of methylene chloride at 25°C is treated with 0.9 g or boron tribromide. The mixture is stirred for about 15 hours at 25°C after which 10 ml of methanol is added and the solvents evaporated. The resulting residue is heated to reflux with 50 ml of 6 N hydrochloric acid for 5 hours. The solution is concentrated, the pH adjusted to 6 and applied to a column of Amberlite 120 H^+. Eluting with 1 M ammonium hydroxide affords 2-acetylene- 2-amino- 3-(3-hydroxyphenyl) propionic acid after recrystallization from water-ethanol.

When in the procedure of Example 5 an appropriate amount of benzyl- chloride, 4-chloro- 2-methoxybenzyl- chloride, 2-chloro- 6-methyl- benzyl- chloride, 2,4-dichloro- 6-methyl- benzyl- chloride, 4-methoxy- 6- methylbenzyl- chloride, or 6-*tert*-butyl- 4-chlorobenzyl- chloride is substituted for 3',4'œ isopropylidene- dioxybenzyl- bromide the following products are obtained:
2-acetylene- 2-amino- 3-phenyl- propionic acid, 2-acetylene- 2-amino- 3-(4-chloro- 2-methoxyphenyl) propionic acid, 2-acetylene- 2-amino- 3-(2-chloro- 6-methylphenyl) propionic acid, 2-acetylene- 2-amino- 3-(2,4-dichloro- 6-methylphenyl)- propionic acid, 2-acetylene- 2-amino- 3-(4-methoxy- 6-methyl) phenyl) propionic acid and 2-acetylene- 2-amino- 3-(6-*tert*-butyl- 4-chlorophenyl) propionic acid.

EXAMPLE 8

Ethyl 2-acetylene- 2-amino- 3-(3,4-dihydroxy- phenyl) propionate hydrochloride

A suspension of 2.2 g (10 mM) of 2-acetylene- 2-amino- 3-(3,4-dihydroxy- phenyl) propionic acid in 30 ml of ethanol is saturated with anhydrous HC1, and the resulting solution allowed to stand at 25°C for 24 hours. The solvent is evaporated leaving a residue which is recrystallized from ethanol-ether to give ethyl 2-acetylene- 2-amino- 3-(3,4-dihydroxy- phenyl) propionic hydrochloride.

EXAMPLE 9

2-Acetylene-3- (3,4-diacetyloxyphenyl)- 2-(tert- butoxy- carbonylamino)- propionic acid

2 N Aqueous sodium hydroxide and acetic anhydride (3.5 g) are added simultaneously during ½ hour to a solution of 2-acetylene- 2-(*tert*- butoxycarbonyl- amino)- 3-(3,4- dihydroxy- phenylpropionic acid (6 g) prepared from 2-acetylene- 2-amino-3- (3,4-dihydroxy- phenyl)propionic acid and *tert*-butyl azidoformate, in 30 ml of 1 N sodium hydroxide under argon so that the pH is maintained between 6.5 and 7.5. After 1 hour at 25°C the pH is adjusted to 1 using 6 N sulfuric acid then extracted with methylene chloride. The organic phase is dried and concentrated to give 2-acetylene- 3-(3,4-diacetyl- oxyphenyl)- 2-*tert*-butoxy- carbonylamino)- propionic acid.

EXAMPLE 10

2-Acetylene- 2-(acetylamino)- 3-(3,4-dihydroxy- phenyl)- propionic acid

To a stirred suspension of 6.8 g (10 mM) of borax in 10 ml of water is added 2.2 g (10 mM) of 2-acetylene- 2-amino-3- (3,4-dihydroxyphenyl)- propionic acid under argon. After 15 minutes the pH is adjusted to 9 by the addition of 2 N sodium hydroxide then treated dropwise with 780 mg of acetyl chloride, maintaining the pH between 9.0 and 9.5. The aqueous solution is washed with ether, adjusted to a pH of 1 using 6 N sulfuric acid and extracted with methylene chloride. The organic phase is dried and concentrated to afford 2-acetylene- 2-(acetylamino)- 3-(3,4- dihydroxyphenyl)- propionic acid, which may be treated with ethanolic HCl to afford the ethyl ester.

EXAMPLE 11

Acetylene- 2-amino-3- (3,4-diacetyloxy- phenyl)- 1-oxo- propylamino}- propionic acid

A solution of 4.4 g (10 mM) of 2-acetylene- 2-carbobenzyl- oxyamino)- 3-(3,4-diacetyl- oxyphenyl)- propionic acid, prepared from 2-acetylene- 2-amino-3- (3,4-diacetyloxy- phenyl)- propionic acid and benzyl chloroformate, in 50 ml of ether is treated with 1.0 g (10 mM) of triethylamine followed by 1.08 g (10 mM) of ethyl chloroformate. After 1 hour at 25°C the precipitate is filtered off and to the ether solution is added a solution of alanine benzyloxy ester (10 mM) in 30 ml of ether. The solution is maintained at 25°C overnight then evaporated to dryness. The residue is treated with HBr in dioxane (40% w/w, 20 ml) for 30 minutes at 25°C. Ether is then added and the precipitated hydrobromide filtered off to give 2-[2-acetylene- 2-amino- 3-(3,4-diacetyl- oxyphenyl)- 1-oxopropyl- amino]propionic acid.

EXAMPLE 12

2-Acetylene- 2-(2-amino- 1-oxopropylamino)- 3-(3,4-dihydroxy- phenyl)propionic acid hydrochloride

A suspension of 3.3 g (10 mM) of benzyl 2-acetylene- 2-amino-3- (3,4-dihydroxy- phenyl)propionate in 50 ml of methylene chloride is treated with 1 g (10 mM) of triethylamine afterwhich 10 mM of N-carbobenzyl-oxyalanine wherein the acid function is activated by ethoxycarbonyl in 20 ml of methylene chloride is added. The mixture is stirred at 25°C for about 16 hours then washed with water. The organic layer is dried and evaporated. The residue is taken up in ether and the ether solution cooled to 0°C. A vigorous stream of HCl gas is bubbled through the solution for 3 hours after which the ether solution is washed with water. The aqueous phase is evaporated to afford 2-acetylene- 2-(2-amino- 1-oxopropylamino)- 3-(3,4-dihydroxy-phenyl)propionic acid hydrochloride as a gum.

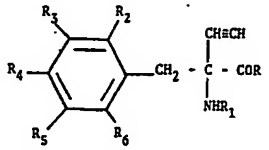
EXAMPLE 13

2-Acetylene- 2-amino-3- (4-hydroxy-3- methoxyphenyl)- propionic acid

A solution of 3.25 g (10 mM) of 2-acetylene- 2-amino-3- (4-benzyloxy- 3-methoxyphenyl)- propionic acid in 20 ml of tetrahydrofuran is added to 100 ml of ammonia at −30°C containing 0.5 g of lithium amide. After 1 hour lithium metal is added until the blue color persists for 20 minutes then ammonium chloride is added, and the ammonia allowed to evaporate. The residue is dissolved in water, the pH adjusted to 6 and applied to an Amberlite 120 H^+ resin. Elution with 1 M ammonium hydroxide affords 2-acetylene- 2-amino-3- (4-hydroxy- 3-methoxyphenyl)- propionic acid which is recrystallized from water.

CLAIMS

1. A compound of the formula



wherein R_1 is hydrogen, (C_{1-4}alkyl)carbonyl, (C_{1-4}alkoxy)- carbonyl or –CO–CHNH$_2$–R_{27} wherein R_{27} is hydrogen, alkyl of 1 to 4 carbon atoms, benzyl or *p*-hydroxy- benzyl; R is hydroxy, alkoxy of 1 to 8 carbon atoms, –NR_7R_8 wherein R_7 and R_8 are the same or different and are each hydrogen or C_{1-4} alkyl or –NH–CHR_9–COOH wherein R_9 is hydrogen, alkyl of 1 to 4 carbon atoms, benzyl or *p*-hydroxy- benzyl; and R_2, R_3, R_4, R_5 and R_6 are as defined in the following table

R_2	R_3	R_4	R_5	R_6
H	$-O-CH_2-O-$		H	H
H	H	H	H	H
H	H	OR_{10}	H	H
H	OR_{10}	H	H	H
H	OR_{10}	OR_{10}	H	H
OR_{10}	H	Cl	H	H
H	OR_{10}	Cl	H	H
Cl	OR_{10}	H	H	H
Cl	OR_{10}	Cl	H	H
Cl, F	H	OR_{10}	H	H
Cl	H	H	H	CH_3
Cl	H	Cl	H	CH_3
H	H	Cl, F	H	CH_3
OR_{10}	H	CH_3	H	CH_3
Cl	H	CH_3	H	CH_3
H	H	OR_{10}	H	CH_3
H	H	OR_{10}	H	C_2H_5
OR_{10}	H	C_2H_5	H	C_2H_5
H	OR_{10}	H	OR_{10}	H
H	OR_{10}	OR_{10}	OR_{10}	H
H	H	OCH_3	OH	H
H	H	OH	OCH_3	H
OR_{10}	OR_{10}	H	H	H
OR_{10}	H	H	H	H
H	H	Cl	H	C_2H_5
H	H	Cl	H	tert-C_4H_9
H	H	OR_{10}	H	tert-C_4H_9

wherein R_{10} is hydrogen, alkyl of 1 to 8 carbon atoms, (C_{1-6}alkyl)- carbonyl, benzoyl or phenyl(C_{1-6}alkyl)-carbonyl; or a pharmaceutically acceptable salt thereof.

2. A compound or salt as claimed in claim 1 wherein R_1 is hydrogen or (C_{1-4}alkyl)- carbonyl.

3. A compound or salt as claimed in claim 1 or claim 2 wherein R is hydroxy or alkoxy of 1 to 8 carbon atoms.

4. A compound or salt as claimed in claim 1 wherein R_1 is hydrogen and R is hydroxy.

5. A compound or salt as claimed in any preceding claim wherein R_2, R_3, R_4, R_5 and R_6 are the same or different and are each hydrogen or OR_{10} wherein R_{10} is hydrogen or alkyl of 1 to 8 carbon atoms.

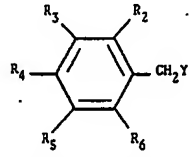
6. A compound or salt as claimed in claim 5 wherein R_{10} is hydrogen.

7. A compound or salt as claimed in claims 1 to 4 wherein R_3 and R_4 are the same or different and are each hydrogen or hydroxy.

8. 2-Acetylene- 2-amino-3- (3,4-dihydroxy- phenyl)propionic acid or a pharmaceutically acceptable salt thereof.

9. 2-Acetylene- 2-amino- 3-(3-hydroxy- phenyl)propionic acid or a pharmaceutically acceptable salt thereof.

10. A process for preparing a compound as claimed in claim 1 when R_1 is hydrogen, R is hydroxy and (i) R_2 and R_3 are each hydroxy, (ii) R_3 and R_4 are each hydroxy, (iii) R_3 and R_4 together are $-O-CH_2-O-$, or (iv) R_2, R_3, R_4, R_5 and R_6 are as defined in claim 1 with the limitation that R_{10} is methyl, which comprises treating a protected propargylamine derivative with a strong base; alkylating the protected propargylamine carbanion intermediate which is formed in a solvent at $-120°$ to 25°C for from 30 minutes to 24 hours, with (i) a 2,3-isopropyl- idenedioxy- benzyl halide, (ii) a 3,4-isopropyl- idenedioxy- benzyl halide, (iii) a 3,4-methylene-dioxybenzyl halide, or (iv) compound of the formula



wherein Y is halogen and R_2, R_3, R_4, R_5 and R_6 are as defined above for group (iv) with the proviso that R_3 and R_4 together are not $-O-CH_2-O-$; treating the thus formed alkylated propargylamine derivative with a strong base; acylating the alkylated propargylamine carbanion which is formed with an acylating reagent in a solvent for from 30 minutes to 24 hours at $-120°$ to 25°C; and hydrolysing the product.

11. A process for preparing a compound or salt as claimed in claim 1 substantially as described in any of

Examples 1 and 5 to 13.

12. A compound or salt as claimed in claim 1 when prepared by a process according to claim 10 or claim 11.

13. A pharmaceutical composition comprising a compound or salt as claimed in any of claims 1 to 9 and 12 in association with a pharmaceutically acceptable excipient.

14. A composition according to claim 13 substantially as described in any of Examples 2 to 4.

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